Remarks

No new issues are raised, and or new matter have been added to the claims, by the foregoing amendments. Therefore, Applicants respectfully request entry and consideration of the foregoing amendments.

Support for the foregoing amendments to the claims may be found throughout the specification. Specifically, support for the amendments to claims 14, 15, 19, 31 and 40 may be found in the specification at pages 62-63 and throughout the Examples; support for new claims 89-101 may be found in the specification at pages 31-42 and throughout the Examples; and support for new claims 102-104 may be found in the specification at pages 20-21, 28-31 and 40-46, throughout the Examples, and in the claims as originally filed. Accordingly, the present amendments do not add new matter, and their entry is respectfully requested.

I. Status of the Claims

By the foregoing amendments, claims 77-80 have been cancelled; claims 14, 15, 18, 19, 31, and 40 have been amended; and new claims 89-104 are sought to be entered. These amendments do not introduce new matter into the application. Upon entry of the foregoing amendments, claims 14-51, 65-76 and 81-104 are pending in the application, with claims 14, 19, 31 and 40 being the independent claims.

II. Summary of the Office Action

In the Office Action, the Examiner has maintained six rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action.

III. The Rejections Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at page 2, the Examiner has maintained the rejection of claims 14-39 and newly rejected claims 65-79, 81-83, and 85-87 under 35 U.S.C. § 112, second paragraph, for being allegedly indefinite. Applicants respectfully traverse this rejection, and reiterate and incorporate herein by reference the remarks concerning this same rejection that were made in Applicants' Amendment and Reply filed in the present matter on March 8, 2001.

A. The Recitation of "Effective Amount"

In maintaining this rejection, the Examiner contends that claims 14, 19 and 31 are vague and indefinite in that the metes and bounds of the terms an "effective amount" are unclear. Applicants respectfully disagree. The meaning of "effective amount" of a ribosomal protein is clearly described in detail in the specification, particularly at page 33, lines 3-23. In addition, the specification provides detailed protocols for titration assays that enable the ordinarily skilled artisan to determine the optimum concentration of a given ribosomal protein for use in the claimed methods (*see, e.g.*, pages 68-76, particularly in Example 1 at pages 71-73, particularly in Tables 3 and 4 at pages 71 and 72, respectively).

Thus, Applicants respectfully assert that one of ordinary skill would readily understand the meaning of "effective amount" of a ribosomal protein based on clear guidance provided in the present specification. However, to expedite prosecution and allowance of the present application, and not in acquiescence to this portion of the rejection, the term "effective amount" has been deleted from claims 14, 19 and 31. Thus, this portion of the rejection has been accommodated; reconsideration and withdrawal are respectfully requested.

B. The Recitation of "Substantially Recombine"

At pages 3-4 of the Office Action, the Examiner has also maintained the contention that claims 14 and 19 are indefinite because the recitation "do not substantially recombine" is allegedly unclear. Applicants respectfully disagree. The phrase "do not substantially recombine" in claims 14 and 19 can be easily understood by the ordinarily skilled artisan reading this phrase, in view of the present specification and information readily available in the art (which, under *Moelands*, must be considered together to determine the definiteness of a claim). Thus it would be within the ability of one of ordinary skill in the art to readily understand the meaning of "do not substantially recombine."

However, to expedite prosecution and allowance of the present application, Applicants have amended the claims to delete the term "substantially." Accordingly, Applicants respectfully request that this portion of the rejection be reconsidered and withdrawn.

IV. The Rejections Under 35 U.S.C. § 102(b) Are Traversed

The Examiner has also maintained the rejection of claims 31-32, 36, 38-51, and has newly rejected claims 65-72, 74-76, 79-80, and 87-88 under 35 U.S.C. § 102(b) as being anticipated by Nash *et al.* (*Meth. Enzymol. 100*:210-216 (1983)) (Doc. No. AS34, of record; hereinafter "Nash"). Office Action at pages 4-6.

In addition, the Examiner has maintained the rejection of claims 40-51, 80 and 88 under 35 U.S.C. § 102(b) as being anticipated by Abremski *et al.* (*J. Biol. Chem. 259*:1509-1514 (1984)) (Doc. No. AS1, of record; hereinafter "Abremski I") and Abremski *et al.* (*J. Biol. Chem. 257*:9658-9662 (1982)) (Doc. No. AR1, of record; hereinafter "Abremski II"). *See* Office Action at page 5-6. Applicants respectfully traverse these rejections, and reiterate and incorporate herein by reference the remarks concerning this same rejection that were made in Applicants' Amendment and Reply filed in the present matter on March 8, 2001. Applicants also wish to offer the following additional remarks.

In maintaining these rejections, the Examiner contends that all three references teach "the 'isolation' of ribosomal and recombinase proteins to varying degrees for use in recombination reaction mixtures." Office Action at page 4, last paragraph, to page 5, second full paragraph. Applicants respectfully disagree.

Applicants respectfully assert that the Examiner's interpretation of the word "isolation" differs from that which has been defined, interpreted and often used by those of ordinary skill in the art in reference to the isolation of proteins. For example, the term "isolation," as defined in Merriam-Webster's Dictionary, means "to set apart from others or to select from among others, *especially* to separate from another substance so as to obtain pure or in a free state." Merriam-Webster Online, www.m-w.com, Merriam-Webster's

Collegiate Dictionary, Merriam-Webster, Inc., 2001 (emphasis in original). Clearly, if any ribosomal proteins are present in the crude extracts disclosed in Nash and in Abremski I and II, they are not "set apart from others" or "pure or in a free state."

Moreover the Examiner further contends that:

> the Nash et al reference teaches that the crude E. coli cell extracts utilized for characterization of the λ int recombinase were generated by lysis of the cell wall/membrane by sonication and centrifugation at 15,000 RPM for 20 minutes to pellet the insoluble debris (e.g. page 212, second full paragraph, *Preparation of crude IHF*). Both of the Abremski et al references teach lysis of E. coli cells by sonication and centrifugation at 17,000 RPM for 30 minutes to generate crude extracts which were assayed for recombinase activity (e.g. see each results section under *Enzyme Purification*). Such cell lysis and centrifugation techniques are and were routinely practiced in the art and are recognized as providing an E. coli cell extract comprising isolated and soluble proteins, including ribosomal polypeptides.

Office Action, at page 6, first full paragraph. Thus, the Examiner alleges that the crude extracts taught by Nash, Abremski I and Abremski II contain ribosomal polypeptides in the crude extracts, thereby anticipating the present claims. Applicants respectfully disagree.

Based on the definition of "isolated" (or its synonym, "purified") discussed above, one of ordinary skill in the art would not consider crude cell extracts to be equivalent to isolated or purified forms of the ribosomal proteins. It is also understood by one of ordinary skill in the art that "crude extracts" are by their very nature *crude*. Therefore, ribosomal proteins, having been extracted in a crude way and being present in crude extracts as in the cited references, are not "in a pure and free state" as the terms "isolated" and "purified" are defined by Webster's Dictionary or as they are consistently used in the art. Therefore, the cited art does not expressly or inherently disclose the presently claimed invention.

In addition, the Examiner has apparently assumed from reading the cited references that it is *possible* that ribosomal proteins are inherently present in the crude extracts used. However, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis added). Therefore, even if it was *possible* that ribosomal proteins were present in the crude extracts used in the cited references, there is no objective indication that ribosomal proteins were *definitely* present therein. The disclosure of crude extracts which may or may not contain ribosomal proteins cannot anticipate claims specifically reciting "isolated" (or "purified") ribosomal protein. Hence, the Examiner's attempted reliance upon inherent anticipation in the present case is factually and legally unfounded.

Accordingly, Applicants respectfully assert that the invention as presently claimed is not anticipated Nash, Abremski I or Abremski II, as none of the cited references disclose the use of purified ribosomal proteins in their methods. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

V. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

The Examiner has maintained the rejection of claims 14-51 and newly rejected claims 65-88 under 35 U.S.C. § 103(a) as being unpatentable over Hartley *et al.* (U.S. Patent No. 5,888,732; hereinafter "Hartley") in view of Nash, or Abremski I, or Abremski II. Office Action at pages 7-9. Applicants respectfully traverse this rejection.

The Examiner contends that:

> methods taught by Hartley et al do encompass in vitro embodiments wherein the recombination enzymes are

> supplied as part of a crude cellular extract following overexpression in bacterial cells. Hartley et al teach each of the other limitations present in the rejected claims (e.g. site specific recombinases used to recombine Insert Donors, Vector donors, etc.). The supporting references cited in the instant rejection provide teachings to indicate that one can practice such methods with crude cellular extracts in order to provide the recombinase proteins along with other cellular factors which can aid recombination (e.g. IHF for Int or Xis mediated recombination).

Office Action at page 8, lines 6-12. Applicants respectfully disagree.

Claims 14-51 and 65-88 are specifically drawn to a method of cloning comprising use of at least one purified ribosomal protein. The Examiner acknowledges that Hartley does not disclose, suggest or contemplate the specific limitations of using purified ribosomal proteins in the claimed method. In fact, in Paper No. 8 (where this rejection was first made), the Examiner acknowledged that Hartley does not teach the use of crude cellular extracts in the recombination methods disclosed therein (*see* Paper No. 8 at page 8, third full paragraph). Therefore, it is unclear why the Examiner contends, in the excerpt above, that the methods taught by Hartley "encompass" *in vitro* methods using crude cellular extracts, since this contention appears to be at odds with the Examiner's acknowledgment of just the opposite in Paper No. 8.

Applicants further note that the Examiner also contends that the supporting references disclose that one can practice the claimed invention by using crude extracts. Applicants reiterate that a general teaching in a reference cannot be a basis of a *prima facie* case of obviousness. The Examiner thus insinuates that crude extracts would inherently contain ribosomal proteins because the crude extracts contain "other cellular factors which can aid recombination." Applicants wish to remind the Examiner, however, that there is no such thing as "inherent obviousness," since inherence and obviousness are different legal

concepts. *See In re Spormann*, 150 USPQ 449, 452 (C.C.P.A. 1966). That which is inherent cannot be obvious, since inherent information "is not necessarily known . . . . [and] Obviousness cannot be predicated on what is unknown." *Id.*

Moreover, the claims as currently presented are specifically directed to methods of recombination using purified ribosomal proteins. The Examiner has not provided evidence to suggest why one of ordinary skill in the art would specifically use isolated or purified ribosomal proteins to aid in recombination, based solely on the disclosures of the cited art, particularly, since none of the cited references discloses or suggests purification of ribosomal proteins for use in recombination reactions. Therefore, the cited art cannot form the basis of a *prima facie* case of obviousness of the present claimed invention.

In addition, the Examiner contends that:

> the motivation for combining the teachings of the primary and secondary references is to receive the expected benefit of providing one or more recombination proteins to the in vitro recombination mixture without the need for further purifying of recombination elements and, in the case of Int/Xis, providing multiple factors known to enhance recombination (e.g. IHF).
>
> * * * *
>
> [T]here is no need for a specific teaching in the supporting references that ribosomal proteins are necessarily present in the crude extracts taught by the supporting references because this is not the basis for combining the references. The supporting references are applicable, however, with regard to the presence of ribosomal proteins in the recombination mixtures of the invention because such ribosomal proteins would <u>necessarily</u> be present in the crude extracts taught by the supporting references . . . Such cell lysis and centrifugation techniques are and were routinely practiced in the art and are recognized as providing an E. coli cell extract comprising isolated and soluble proteins, including ribosomal polypeptides.

Office Action, page 8, line 20 to page 9, line 1, and page 9, lines 6-20 (emphasis in original). Applicants respectfully disagree. The Examiner is reminded that the teaching, suggestion or motivation to combine references must be found either in the references themselves or in general knowledge available to one of ordinary skill in the art. *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The Examiner has acknowledged this requirement, stating that:

> the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Office Action, at page 8, lines 15-18. In making this rejection, however, the Examiner has attempted to rely on a motivation to combine the cited references without providing evidence in any of the cited references as to the source of this motivation. There is no disclosure, suggestion or contemplation that would have motivated one of ordinary skill in the art to specifically choose isolated or purified ribosomal proteins in recombination methods, instead of the crude extracts actually disclosed in these references. Moreover, the use of isolated or purified ribosomal proteins in recombination reactions was not known in the art at the time of the claimed invention. Therefore, it could not have been obvious to one of ordinary skill in the art to use isolated or purified ribosomal proteins in recombination reactions, instead of the crude extracts disclosed in the cited art. Since obviousness cannot be predicated on what is unknown, *see Spormann*, 150 USPQ at 452, the presently claimed invention using purified ribosomal proteins could not possibly have been obvious.

Moreover, when examining a claim for non-obviousness, an Examiner is required to examine a claim as a whole, not just a single element or elements of the claim. *See* MPEP § 2141.02. That is, the Examiner is required to determine whether the prior art suggests the

claim as a whole. What the Examiner has done in this case is look to "a general idea" of a single element or elements of the claimed method, which is improper. Here, the general idea alleged by the Examiner is that crude extracts can be used in place of isolated or purified ribosomal proteins. However, the present claims are not drawn to a "general idea" but are drawn to methods of cloning or subcloning using purified ribosomal proteins in the reaction mixtures. Since the Examiner has failed to provide evidence as to why one of ordinary skill in the art would have preferred purified ribosomal proteins over the crude extracts as disclosed by Hartley, Nash, Abremski I and Abremski II, a *prima facie* case of obviousness cannot be established based on these references. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

VI. The Double Patenting Rejection

The Examiner has rejected claims 14-51 and 65-88 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37 of Hartley. *See* Office Action at page 11, first full paragraph. Applicants respectfully traverse this rejection, and respectfully disagree with the Examiner's contentions for the reasons given above concerning the disclosure of Hartley, which are reiterated and incorporated by reference herein.

In making the rejection, the Examiner contends that:

> [r]ejection of the instant claims as not being patentable over the claims of [Hartley] was not based upon any inherency argument with regard to [Hartley]. The rejection was based upon the fact that the claims embrace in vitro embodiments wherein a crude cellular extract is used to provide recombination proteins and/or other factors to the recombination mixture and that such extracts would necessarily comprise ribosomal proteins (see above).

Office Action at page 11, last full paragraph at lines 4-9. Applicants respectfully disagree. As discussed above, and as the Examiner has previously acknowledged (*see* Paper No. 8 at page 8), Hartley does not disclose the use of "crude extracts." Thus, any double patenting rejection based on this contention is in error.

Moreover, even assuming *arguendo* that Hartley *did* disclose the use of crude extracts, the Examiner's contention that such crude extracts would necessarily comprise ribosomal polypeptides is based on assumptions without evidence or scientific fact. The Examiner has implied that crude extracts allegedly disclosed by Hartley (which, as noted above, are *not* disclosed by Hartley) inherently comprise ribosomal proteins. Applicants wish to remind the Examiner, however, that there is no such thing as "inherent obviousness," since inherence and obviousness are different legal concepts. *See Spormann*, 150 USPQ at 452. Therefore, the Examiner has not provided evidence or scientific fact that ribosomal proteins are necessarily present in the crude extracts allegedly disclosed by Hartley (which, in fact, are *not* disclosed by Hartley), but is basing this rejection, instead, on mere assumptions alone.

In addition, the claims of Hartley are drawn to a method of recombination using recombination protein and recombination sites (see specifically claim 29-37). However, these claims do not recite the use of purified or isolated ribosomal proteins. At most, claims 29-73 of Hartley are drawn to a generic method that encompasses the present invention as a species drawn to such methods using purified or isolated ribosomal proteins. The disclosure of a genus does not necessarily render obvious any species that happens to fall within it. *See In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). In making this

rejection, the Examiner has not provided evidence as to why the skilled artisan would specifically select purified ribosomal proteins instead of crude extracts for use in recombination reactions. Absent such evidence, the Hartley disclosure cannot be used in an obviousness-type double patenting rejection, since there is no evidence that the presently claimed invention would have been obvious over Hartley.

In view of the foregoing remarks, Applicants respectfully assert that the presently claimed invention is patentably distinct over the claims of Hartley. Reconsideration and withdrawal of the obviousness-type double patenting rejection are therefore respectfully requested.

VII. Other Matters

Applicants acknowledge receipt of the Examiner-initialed copy of the Forms PTO-1449 submitted with Applicants' First and Second Supplemental Information Disclosure Statements (IDS) filed in the present matter on March 8, 2001 and April 9, 2001, respectively. However, Applicants have not received the Examiner-initialed copy of the Forms PTO-1449 submitted with Applicants' IDS filed on September 18, 2000, indicating that courtesy copies of unlocated documents AT1, AS4, AT4, AR5, AR9, AR19, AT21, AS22, AS24, AS26, AS29, AR32, AS32, AR35, AT36, AS38, AT40, AR46, AS46, AR47, AR49, AS49, AR50, AS52, AR53, AR54, AR57, AT58 and AS59-AS62 have been considered. Courtesy copies of these documents were resubmitted with Applicants' Amendment and Reply filed on March 8, 2001, along with a copy the Form PTO-1449 that was filed on September 18, 2000. It is respectfully requested that the Examiner initial and return a revised copy of the Form PTO-1449 that was filed in the present matter on

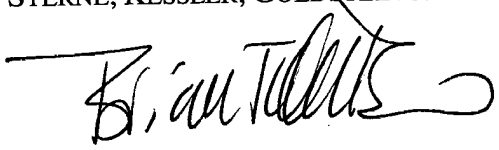
September 18, 2000, and indicate in the official file wrapper of this patent application that these specific documents have been considered.

VIII. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Version with markings to show changes made

(a) Claims 77-80 are cancelled, without prejudice or disclaimer.

(b) Claims 14, 15, 18, 19, 31 and 40 have been amended as follows:

14. (Twice amended) A method for cloning or subcloning one or more desired nucleic acid molecules comprising

(a) forming a [combination] mixture by combining *in vitro*

(i) one or more [Insert Donor] first nucleic acid molecules comprising one or more desired nucleic acid segments flanked by at least two recombination sites, wherein said recombination sites do not [substantially] recombine with each other;

(ii) one or more [Vector Donor] second nucleic acid molecules each comprising at least two recombination sites, wherein said recombination sites do not [substantially] recombine with each other;

(iii) [an effective amount of] at least one recombination protein; and

(iv) [an effective amount of] at least one purified ribosomal protein; and

(b) incubating said [combination] mixture under conditions sufficient to transfer one or more of said desired segments into one or more of said [Vector Donor] second nucleic acid molecules, thereby producing one or more desired [Product] third nucleic acid molecules.

15. (Twice amended) The method of claim 14, further comprising:

(c) forming a [combination] mixture by combining *in vitro*

(i) one or more of said [Product] third molecules comprising said desired segments flanked by two or more recombination sites, wherein said recombination sites do not [substantially] recombine with each other;

(ii) one or more different [Vector Donor] fourth nucleic acid molecules each comprising two or more recombination sites, wherein said recombination sites do not [substantially] recombine with each other;

(iii) [an effective amount of] at least one recombination protein; and

(iv) [an effective amount of] at least one purified ribosomal protein; and

(d) incubating said [combination] mixture under conditions sufficient to transfer one or more of said desired segments into one or more different [Vector Donor] fourth nucleic acid molecules, thereby producing one or more different [Product] fifth nucleic acid molecules.

18. (Once amended) The method of claim 14, further comprising incubating said different [Product] third nucleic acid molecules with one or more different [Vector Donor] fourth nucleic acid molecules under conditions sufficient to transfer one or more of said desired segments into said different [Vector Donor] fourth nucleic acid molecules.

19. (Twice amended) A method for cloning or subcloning desired nucleic acid molecules comprising:

(a) forming a [combination] mixture by combining *in vitro*

(i) one or more [Insert Donor] first nucleic acid molecules comprising one or more nucleic acid segments flanked by two or more recombination sites, wherein said recombination sites do not [substantially] recombine with each other;

(ii) two or more different [Vector Donor] second nucleic acid molecules each comprising two or more recombination sites, wherein said recombination sites do not [substantially] recombine with each other;

(iii) [an effective amount of] at least one recombination protein; and

(iv) [an effective amount of] at least one purified ribosomal protein; and

(b) incubating said [combination] mixture under conditions sufficient to transfer one or more of said desired segments into said different [Vector Donor] second nucleic acid molecules, thereby producing two or more different [Product] third nucleic acid molecules.

31. (Twice amended) A method for recombinational cloning of one or more desired nucleic acid molecules comprising:

(a) forming a mixture by mixing *in vitro* one or more of said desired nucleic acid molecules with one or more vectors and with [an effective amount of] at least one purified ribosomal protein and [an effective amount of] at least one recombination protein; and

(b) incubating said mixture under conditions sufficient to transfer said one or more desired nucleic acid molecules into one or more of said vectors.

40. (Twice amended) A method for enhancement of recombinational cloning, comprising contacting at least two nucleic acid molecules each comprising at least one recombination site *in vitro* with one or more purified ribosomal proteins and with one or more recombination proteins to form a mixture, and incubating said mixture under conditions favoring the production of at least one product nucleic acid molecule.

(c) New claims 89-104 are sought to be entered.